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1. Your reference 46299.GB01/NT

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2. Patent application number *(The Patent Office will fill in this part)* 13 JUN 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

The Babraham Institute
Babraham Hall
Babraham
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CB2 4AT
United Kingdom

Patents ADP number *(if you know it)*

7414519002

If the applicant is a corporate body, give the country/state of incorporation United Kingdom

4. Title of the invention

Diagnosis of Schizophrenia

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

91001

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Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

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Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Reddie & Grose Date 13 June 2003

Reddie & Grose

12. Name and daytime telephone number of person to contact in the United Kingdom

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Diagnosis of Schizophrenia

This invention relates to methods of diagnosis of schizophrenia (SZ), and to methods for the prevention, treatment, or amelioration of SZ.

SZ is a severe psychiatric disorder characterized by hallucinations, delusions, disorganized thought, and various cognitive impairments. Polygenic models of inheritance and linkage analysis studies have postulated that several genes confer susceptibility to SZ. Hakak *et al* (PNAS, 2001, 98 (8) 4746-4751) have reported that the expression levels of genes involved in neuronal myelination, development, synaptic plasticity, neurotransmission, and signal transduction were altered in the dorsolateral prefrontal cortex of SZ brain tissue. Mimmack *et al* (PNAS, 2002, 99 (7) 4680-4685) have found significant up-regulation of several members of the apolipoprotein L family in the prefrontal cortex of schizophrenia brains. Middleton *et al* (Journal of Neuroscience, 2002, 22 (7) 2718-2729) have identified alterations of specific metabolic pathways in schizophrenia. However, the molecular basis of schizophrenia is only beginning to be understood. This has hampered reliable diagnosis and effective treatment of the disorder.

We have identified abnormalities in the expression levels of several genes in the prefrontal cortex of patients with schizophrenia compared with control samples. In particular, the expression level of the following genes was observed to be decreased in the prefrontal cortex of schizophrenia patients:

PARG;OLR1; ARPC3; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1;

Ornithine related genes: OAT; OAZIN; OAZ2;

Arginine related genes: ARG2;

ATP synthase (mitochondrial) genes: ATP6V1B2; ATP6IP2; ATP6V1C1;

ATP synthase (vacuolar) genes: ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1;

Complex 1 genes: NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4;

Complex 3 genes: UQCRH; UQCRFS1; UQCRC2; UQCRB; UQCRC2;
Complex 4 genes: COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1;
COX7BP1;
Holocytochrome c Synthetase genes: HCCS;
Adenine translocators genes: SLC25A4
Voltage dependent anion channels (in mitochondrial outer-membrane) genes:
VDAC2; VDAC1P; VDAC3;
Lactate metabolism genes: LDHB; LDHA;
Isocitrate dehydrogenase genes: IDH3B; IDH3A
HMG related genes: HMGCR
Glutamate metabolism genes: GLRX2.

The expression level of the following genes was observed to be increased in the prefrontal cortex of schizophrenia patients:
FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2;
purine metabolism (matrix) genes: ALDH4A1; PYCR1;
metallo proteins genes: MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F;
Arginine related genes: DDAH2;
Glycine/Serine metabolism genes: AMT;
HMG related genes: HMGCL;
Oxide related genes: EPHX1.

Table 1 gives the fold changes in expression of the above genes in the prefrontal cortex of schizophrenia brains compared with control samples, and includes Unigene, ReSeq, and Genbank details, and descriptions of the genes, including synonyms.

Many of the changes are mitochondrial changes. These are illustrated schematically in Figure 1. The changes include changes in ROS stress systems (see the Example).

We have carried out cluster analysis, filtering on oxidative stress and mitochondrial genes and found that 90% separation of schizophrenics from controls is achieved if expression of the following genes is downregulated: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251;

KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; and expression of the following genes is upregulated: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

Thus, the reliability of diagnosis of schizophrenia should be dramatically increased by determining the expression levels of the majority, preferably all, of these genes.

According to the invention there is provided a method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the expression level of the majority (preferably all) of the following genes, or the levels of the majority (preferably all) of the proteins encoded by the following genes in a biological sample obtained from the subject, or in a sample derived from a biological sample obtained from the subject: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

If the level of the proteins or expression products in the brain is abnormal (for example compared with control samples from non schizophrenic brains), the subject is diagnosed as either having schizophrenia, or being at risk of developing schizophrenia.

In particular, the subject is diagnosed as either having schizophrenia, or being at risk of developing schizophrenia, if the expression level of the majority (preferably all) of the following genes, or the level of the majority (preferably all) of the proteins encoded by the following genes is reduced compared to a normal subject: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; and the expression level of the majority (preferably all) of the following genes, or the level of the majority (preferably all) of the proteins encoded by the following genes is increased compared

to a normal subject: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

The term "majority" used herein means more than 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, most preferably all.

It is expected that upto 90% reliability of diagnosis of schizophrenia can be achieved by such methods.

The biological sample may comprise any of the following: CNS tissue, brain tissue, cells isolated from the prefrontal cortex, cells isolated from the developing neuroepithelium; a neural stem cell; a progenitor cell.

Cells isolated from the developing human neuroepithelium can be isolated in culture and grown as aggregates termed neurospheres (Svendsen CN, and Smith AG, *Trends Neurosci* 1999 Aug; 22(8): 357-64). These contain a mixture of neural stem and progenitor cells, can be propagated in culture for extended time periods, and hold potential as a source of tissue for repairing the damaged CNS. According to the invention, the sample derived from the biological sample may be a neurosphere.

Preferably the biological sample comprises peripheral tissue or a peripheral cell type in which the level of the protein, or the expression level of the gene, correlates with the level of the corresponding protein, or the expression level of the corresponding gene, in the prefrontal cortex.

Suitable peripheral tissue may comprise blood (consisting of plasma and blood cells). It is possible that a correlated level of protein, or correlated gene expression, may occur in one or more types of blood cell but not in others. In this case, it may be necessary to use blood cells of that type, or those types, which have been separated at least from some of the types of blood cells that do not have correlated levels or correlated expression. If a correlated level of protein, or correlated gene expression, occurs in more than one type of blood cell, blood cells of each type could be separated and, if necessary, pooled together for the determination.

A correlated level of protein, or correlated gene expression may occur in erythrocytes (red cells), platelets, or leukocytes (granulocytes: neutrophils, eosinophils, or basophils; or lymphoid cells: lymphocytes or monocytes).

Methods of determining the expression level of a gene are well known to those of ordinary skill in the art. For example, this may be achieved by determining the level of mRNA or protein expressed from the gene in the biological sample.

Examples of suitable methods for determining the level of mRNA expression are quantitative PCR (in particular, real-time quantitative PCR) performed on cDNA produced by reverse transcription of the mRNA, and Northern blotting.

In a preferred method of determining the level of mRNA expressed, total RNA is obtained from the biological sample, cDNA is synthesized from mRNA of the gene, and the cDNA is used for real-time quantitative PCR analysis to determine the level of the mRNA in the sample.

Examples of suitable methods for determining the level of protein expression are Western blotting and enzyme-linked immunosorbent assay (ELISA).

A binding partner of an expression product of the gene, may be used to detect the level of that expression product. The binding partner may be a protein, preferably an antibody or antibody fragment. The antibody or antibody fragment should bind specifically to the expression product so that the level of the expression product in the biological sample can be determined.

The binding partner may be a nucleic acid capable of hybridizing to a nucleic acid expression product of the gene. The nucleic acid should hybridize specifically (for example under conditions of high stringency) to the nucleic acid expression product so that the level of the nucleic acid expression product in the biological sample can be determined. A preferred nucleic acid binding partner is an oligonucleotide primer for the synthesis of cDNA by reverse transcription from mRNA of the gene.

The level of a nucleic acid expression product of the gene is preferably determined by amplification of that nucleic acid expression product, for example by PCR. Thus, primers capable of amplifying the nucleic acid expression product are provided. Nucleic acid capable of hybridizing (preferably under conditions of high stringency) to nucleic acid that is complementary to a nucleic acid expression product of the gene and/or nucleic acid which is a binding partner (preferably under conditions of high stringency) of an expression product of the gene may be used to amplify a nucleic acid expression product of the gene, for example to detect an expression product of the gene.

There is also provided according to the invention a kit for the diagnosis of schizophrenia that comprises means for detecting the protein or expression products of the majority (preferably all) of the genes listed above in relation to methods of the diagnosis of the invention. Each detecting means may comprise a binding partner of the protein, and/or a nucleic acid capable of hybridizing to nucleic acid that is complementary to a nucleic acid expression product of the gene. According to a preferred embodiment, the expression levels may be determined using a gene chip.

According to the invention there is also provided a gene chip for use in a method of diagnosis of the invention, the gene chip comprising a plurality of different probes capable of hybridising to nucleic acid expression products of the majority (preferably all) of the following genes: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

There is also provided according to the invention a method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the expression level of the majority (preferably all) of following genes, or the levels of the majority (preferably all) of the proteins encoded by the following genes in the brain (preferably the prefrontal cortex) of the subject: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

There is further provided according to the invention a method of prevention, treatment, or amelioration of schizophrenia which comprises increasing the level or activity of the majority (preferably all) of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6;

ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; and reducing the level or activity of the majority (preferably all) of the following proteins in the brain (in particular the prefrontal cortex) of the subject: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

The level of a protein may be altered by gene therapy. The level of a protein may be altered by use of a regulator of expression of a gene coding for the protein.

Experiments which are the basis of the invention are described in the following example, with reference to the accompanying drawings in which:

Figure 1 shows mitochondrial changes associated with schizophrenia;

Figure 2 shows sample quality control steps;

Figure 3 shows data quality control steps;

Figures 4 and 5 show clustering analysis between control (C) and schizophrenia (S) samples; and

Figure 6 shows oxidative buffering.

Example

Integrating Transcriptomics, Proteomics, and Classical Genetics: Fishing in modern neuropsychiatric research

Affymetrix® GeneChip® Post-Mortem Brain Studies

HG-U133 set includes:

- 39,000 probes
- 33,000 annotated
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- Each w/ ~23,000 genes on 1.28 cm^2

Our Studies:

- 150 PM human brain samples from SMRI
- Completed on HG-U133A chips and continuing on B
- Extensive Quality Control(QC) steps
- Cluster analysis

Sample QC Steps (see Figure 2):

Total RNA is screened for degraded samples
cRNA is generated and screened for poor modal length

- Poor samples are run on Test3 GeneChips®
- Prisitine samples are run on U133 GeneChips®

Microarrays are put through our in-house Data QC screen and only "clean" data sets are retained, poor set samples are rerun or rejected

Data QC Steps (see Figure 3):

6 data filters

- RNA digestion plots
- Box plots
- 2 D-chip screens
- In-house parameter script
- In-house heuristic meta-analysis script

Data Mining

- Flag Filtering
- Fold Difference and Significance Filtering
- Subset Significant Gene Overlapping
- Pathway Specific Filtering

Cluster Analysis (see Figures 4 and 5)

Initial Clustering (17,886 genes)

Patients begin to separate …

Until the trees begin to separate large groups of patients on a large gene scale (392 genes)

Filtering on oxidative stress and mitochondrial genes (35 genes)

- 82% separation for C in S
- 90% separation for S in C

Mitochondrial Involvement: Evidence for ROS stress (see Figure 6)

Oxidative Stress: Evidence for Stress Response

Up-regulations in MT transcripts

Changes in specific ROS stress systems including:

- SOD's
- MSR
- GLRX
- PDCD's
- Specific RAS pathways
- HIF's
- Fe containing molecules

Changes in DNA repair mechanisms

Future Directions

- Continue data mining of Affymetrix® results
- Validate gene hits via Q-PCR and poly-"omics"
- Genotyping and SNP analysis of genes that separate patient groups
- GeneChip analysis of peripheral tissues including liver, spleen, blood and duramata

Table 1

Significant clustering 90% separation of schizophrenics from controls	Systematic	Common	Genbank	Map	UniGene	GeneSpring Norm Fold S		ttest S-C	Dchip Norm Fold S		ttest S-C	Description
	205060_at	PARG	NM_003631	10q11.23	Hs.91390	1.510748	Down	3.7332E-05	1.1881727	Down	0.0160033	Homo sapiens poly (ADP-ribose) glycohydrolase (PARG), mRNA.
	211662_s_at	VDAC2	L08666	10q22	Hs.78902	1.12617	Down	0.014133987	1.1240978	Down	0.0034869	Homo sapiens voltage-dependent anion channel 2 (VDAC2), mRNA.
	210004_at	OLR1; OLR1; LOX1; LOX-1; SCARE1	AF035776	12p13.2-p12.3	Hs.77729	1.377409	Down	0.004073548	1.2097276	Down	0.0027743	synonyms: LOX1, LOX-1, SCARE1; scavenger receptor class E, member 1; Homo sapiens oxidised low density lipoprotein (lectin-like) receptor 1 (OLR1), mRNA.
	208736_at	ARPC3; ARPC3; ARC21; p21-Arc	AF004561	12q24.11	Hs.283750	1.285561	Down	5.21013E-05	1.1353506	Down	0.0402546	synonyms: ARC21, p21-Arc; ARP2/3 protein complex subunit p21; Homo sapiens actin related protein 2/3 complex, subunit 3, 21kDa (ARPC3), mRNA.
	208909_at	UQCRFS1; UQCRFS1; RIS1	BC000649	19q12-q13.1	Hs.3712	1.168573	Down	0.01259279	1.2116709	Down	0.0002244	synonym: RIS1; Homo sapiens ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1 (UQCRFS1), nuclear gene encoding mitochondrial protein, mRNA.
	217976_s_at	DNCLI1	NM_016141		Hs.266483	1.334079	Down	6.56512E-05	1.2670291	Down	0.0003879	Homo sapiens dynein, cytoplasmic, light intermediate polypeptide 1 (DNCLI1), mRNA.

203968_s_at	PPM1A; PPM1A; PP2CA; MGC9201; PP2C-ALPHA	NM_021003		Hs.57764	1.331601	Down	3.751E-03	1.1780789	Down	0.0028356	synonyms: PP2CA, PP2C-ALPHA, MGC9201; isoform 1 is encoded by transcript variant 1 and 3; protein phosphatase 2C alpha isoform; Homo sapiens protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), transcript variant 1, mRNA.; synonyms: PP2CA, PP2C-ALPHA, MGC9201; isoform 2 is encoded by transcript variant 2; protein phosphatase 2C alpha isoform; Homo sapiens protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), transcript variant 2, mRNA.; synonyms: PP2CA, PP2C-ALPHA, MGC9201; isoform 1 is encoded by transcript variant 1 and 3; protein phosphatase 2C alpha isofom; Homo sapiens protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), transcript

218871_s_at	ATPIF1; ATPIF1; MGC1167; MGC8898	NM_016311	1p35.3	Hs.24133 5	1.158111	Down	0.0162292648	1.1668271	Down	0.0163228	synonyms: MGC8898, MGC1167, ATPI; isoform 1 is encoded by transcript variant 1; Homo sapiens ATPase inhibitory factor 1 (ATPIF1), transcript variant 1, nuclear gene encoding mitochondrial protein, mRNA.; synonyms: MGC8898, MGC1167, ATPI; isoform 2 is encoded by transcript variant 2; Homo sapiens ATPase inhibitory factor 1 (ATPIF1), transcript variant 2, nuclear gene encoding mitochondrial protein, mRNA.; synonyms: MGC8898, MGC1167, ATPI; isoform 3 is encoded by transcript variant 3; Homo sapiens ATPase inhibitory factor 1 (ATPIF1), transcript variant 3, nuclear gene encoding mitochondrial protein, mRNA.
219833_at	GLRX2; GLRX2; GRX2	NM_016069	1q31.2-q31.3	Hs.5054	1.214861	Down	0.000930749	1.237224	Down	0.0001692	synonym: GRX2; thioltransferase; contains nuclear membrane localisation; CGI-133 protein; Homo sapiens glutaredoxin 2 (GLRX2), mRNA.
215171_s_at	TIMM17A; TIMM17A; TIM17; TIM17A	AK023063	1q32.1	Hs.20716	1.223866	Down	0.000427331	1.2246004	Down	0.0004323	synonyms: TIM17, TIM17A; Homo preprotein translocase; Homo sapiens translocase of inner mitochondrial membrane 17 homolog A (yeast) (TIMM17A), mRNA.

210418_s_at	IDH3B; IDH3B; H-IDHB; MGC903; FLJ11043	AF023265	20p13	Hs.155410	1.167609	Down	0.009473711	1.1832137	Down	0.0036835	synonyms: H-IDHB, MGC903, FLJ11043; isocitric dehydrogenase; NAD+-specific isocitrate dehydrogenase beta precursor; NAD+-specific isocitrate dehydrogenase b subunit; NAD+-specific ICDH; isocitrate dehydrogenase, NAD(+)-specific, mitochondrial, beta subunit; Homo sapiens isocitrate dehydrogenase 3 (NAD+) beta (IDH3B), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.
203946_s_at	ARG2	U75667	14q24.1-q24.3	Hs.172851	1.241001	Down	0.008993809	1.1794939	Down	0.0060619	kidney arginase; nonhepatic arginase; L-arginine amidinohydrolase; L-arginine ureahydrolase; A-II; Homo sapiens arginase, type II (ARG2), nuclear gene encoding mitochondrial protein, mRNA.
200880_at	DNAJA1	AL534104	9p13-p12	Hs.94	1.255584	Down	0.000175313	1.2676009	Down	5.252E-05	DnaJ (Hsp40) homolog, subfamily A, member 1
213921_at	SST; SST; SMST	NM_001048	3q28	Hs.12409	1.616051	Down	0.000215427	1.538124	Down	7.312E-05	synonym: SMST; Homo sapiens somatostatin (SST), mRNA.

210014_x_at	IDH3B; IDH3B; H-IDHB; MGC803; FLJ11043	AF023268	20p13	Hs.15541 0	1.122301	Down	0.019203203	1.121091	Down	0.07916	synonyms: H-IDHB, MGC803, FLJ11043; isocitric dehydrogenase; NAD+-specific isocitrate dehydrogenase beta precursor; NAD+-specific isocitrate dehydrogenase b subunit; NAD+-specific ICDH; subunit; NAD+-specific isocitrate dehydrogenase, NAD(+)-specific, mitochondrial, beta subunit; Homo sapiens isocitrate dehydrogenase 3 (NAD+) beta (IDH3B), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.
220045_at	NEUROD6; NEUROD6; Atoh2; NEX1M; Math-2	NM_022728		Hs.45162	1.267808	Down	0.008816781	1.372238	Down	8.878E-05	synonyms: Atoh2, NEX1M, Math 2; Homo sapiens neurogenic differentiation 6 (NEUROD6), mRNA.
203338_s_at	ICAP-1A	AL548383	2p25.2	Hs.17327 4	1.316151	Down	0.000469971	1.357168	Down	1.018E-05	integrin cytoplasmic domain-associated protein 1
218289_s_at	FLJ23251	NM_024818	3q22.1	Hs.17073 7	1.16494	Down	0.022580668	1.159248	Down	0.0060202	Homo sapiens hypothetical protein FLJ23251 (FLJ23251), mRNA.
204679_at	KCNK1; KCNK1; DPK; HOHO; TWIK1; TWIK-1	NM_002245	1q42-q43	Hs.79351	1.263524	Down	0.000834664	1.268284	Down	3.532E-05	synonyms: DPK, HOHO, TWIK1, TWIK-1; potassium inwardly-rectifying channel, subfamily K, member 1; potassium channel, subfamily K, member 1 (TWIK-1); Homo sapiens potassium channel, subfamily K, member 1 (KCNK1), mRNA.

202825_at	SLC25A4; SLC25A4; T1; ANT; ANT1; PEO2; PEO3	NM_001151	4q35	Hs.2043	1.263055	Down	0.003765193	1.1702885	Down	0.0041136	synonyms: T1, ANT, ANT1, PEO2, PEO3; adenine nucleotide translocator 1 (skeletal muscle); Homo sapiens solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), nucleotide translocator), nuclear member 4 (SLC25A4), nuclear gene encoding mitochondrial protein, mRNA.
218574_at	FLJ13611	NM_024941	5q12.2	Hs.28295 8	1.280891	Down	3.837725-05	1.1867894	Down	0.0110945	Homo sapiens hypothetical protein FLJ13611 (FLJ13611), mRNA.
218948_at	HIRIP5; HIRIP5; CGI-33	NM_016700	2p15-p13	Hs.43043 9	1.20213	Down	0.0000560488	1.2521906	Down	8.482E-05	synonym: CGI-33; HIRIP5 protein; HIRA-interacting protein 5; Homo sapiens HIRA interacting protein 5 (HIRIP5), mRNA.
201597_at	COX7A2; COX7A2; COX7AL; COX7AL1; COXVIIa-L	NM_001865	6q12	Hs.70312	1.149356	Down	0.007904477	1.182426	Down	1.847E-05	synonyms: COX7AL, COX7AL1, COXVIIa-L; hepatic cytochrome-c oxidase chain VIIa; Homo sapiens cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein, mRNA.
203663_s_at	COX5A; COX5A; VA; COX-VA	NM_004255	15q25	Hs.32383 4	1.187843	Down	0.0043798227	1.2284326	Down	7.246E-05	synonyms: VA, COX, COX-VA; cytochrome c oxidase polypeptide, mitochondrial precursor; Homo sapiens cytochrome c oxidase subunit Va (COX5A), nuclear gene encoding mitochondrial protein, mRNA.

206552_s_at	TAC1; TAC1; NK2; NKNA; TAC2	NM_003182	7q21-q22	Hs.2563	1.682809	Down	2.27261E-07	1.6689386	Down	2.145E-08	synonyms: NK2, NKNA, TAC2; neurokinin A; neurokinin alpha; tachykinin 2; substance K; neuropeptide K; neuropeptide gamma; substance P; neurokinin 1; neurokinin 2; neuromedin L; Homo sapiens tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) (TAC1), transcript variant beta, mRNA.; synonyms: NK2, NKNA, TAC2; neurokinin A; neurokinin alpha; tachykinin 2; substance K; neuropeptide K; neuropeptide gamma; substance P; neurokinin 1; neurokinin 2; neuromedin L; Homo sapiens tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) (TAC1), transcript variant alpha,
202233_s_at	UQCRH	NM_006004		Hs.73818	1.148508	Down	0.025105827	1.1682167	Down	3.687E-05	Homo sapiens ubiquinol-cytochrome c reductase hinge protein (UQCRH), mRNA.
218573_at	MAGEH1; MAGEH1; APR-1	NM_014061	Xp11.22	Hs.279819	1.167534	Down	0.018662092	1.2202681	Down	3.034E-05	synonym: APR-1; restin; MAGE-H1 antigen; Homo sapiens APR-1 protein (MAGEH1), mRNA.

217769_s_at	C13orf12; C13orf12; HSPC014; 2510048O06Rik	NM_015932	13q12.13	Hs.27881 3	1.144417	Down	0.009888431	1.1710336	Down	5.867E-05	synonyms: HSPC014, 2510048O06Rik; Homo sapiens chromosome 13 open reading frame 12 (C13orf12), mRNA.
201323_at	EBNA1BP2; EBNA1BP2; P40; EBP2; NOBP	NM_006824	1p35-p33	Hs.34886 8	1.13858	Down	0.018139164	1.1689036	Down	4.637E-05	synonyms: P40, EBP2, NOBP; cell proliferation-associated protein; nucleolar protein p40; homolog of yeast EBNA1-binding protein; nuclear FGF3 binding protein; EBNA1-binding protein 2; Homo sapiens EBNA1 binding protein 2 (EBNA1BP2), mRNA.
219619_at	DIRAS2; DIRAS2; Di-Ras2; DKFZp761C071 21	NM_017594	9q22.1	Hs.16563 6	1.28122	Down	3.394755-05	1.2324031	Down	1.828E-05	synonyms: Di-Ras2, DKFZp761C07121; member of the Ras familysmall GTP-binding protein; Homo sapiens DIRAS family, GTP-binding RAS like 2 (DIRAS2), mRNA.
213924_at	MPPE1	BF476502	18p11.21	Hs.15414 5	1.19454	Down	0.004053367	1.1134948	Down	0.0862616	metallo phosphoesterase
218255_s_at	FBS1; FBS1; FLJ11618	NM_022452	16p11.2	Hs.77735	1.308393	Up	5.96696E-05	1.2607698	Up	4.124E-05	synonyms: FBS, FLJ11618; likely ortholog of mouse fibrosin; Homo sapiens fibrosin 1 (FBS1), mRNA.
202908_at	WFS1; WFS1; WFRS; DFNA6; DFNA14; DFNA38; DIDMOAD; WOLFRAMIN	NM_006005	4p16	Hs.28077	1.264466	Up	1.9637E-05	1.2121222	Up	0.0018794	synonyms: WFS, WFRS, DFNA6, DFNA14, DFNA38, DIDMOAD, WOLFRAMIN; Homo sapiens Wolfram syndrome 1 (wolframin) (WFS1), mRNA.
214203_s_at	PRODH	AA074145	22q11.21	Hs.34387 4	1.410038	Up	0.003550935	1.1914315	Up	0.0336575	proline dehydrogenase (oxidase) 1

204294_at	AMT; AMT; GCE; NKH; GCST	NM_000481	3p21.2-p21.1	Hs.102	1.20989	Up	0.0003991536	1.0981118	Up	0.0102842	synonyms: GCE, NKH, GCST; Homo sapiens aminomethyltransferase (glycine cleavage system protein T) (AMT), mRNA.
209275_s_at	CLN3; CLN3; BTS	AF015593	16p12.1	Hs.19466 0	1.194667	Up	0.0102213866	1.1260952	Up	0.0775445	synonym: BTS; Homo sapiens ceroid-lipofuscinosis, neuronal 3, juvenile (Batten, Spielmeyer-Vogt disease) (CLN3), mRNA.
209600_s_at	ACOX1; ACOX1; MGC1198; PALMCOX	S69188	17q24-17q25	Hs.37939 1	1.271366	Up	0.0033865436	1.1690976	Up	0.0599128	synonyms: ACOX, PALMCOX, MGC1198; acyl-coenzyme A oxidase 1; Homo sapiens acyl-Coenzyme A oxidase 1, palmitoyl (ACOX1), transcript variant 1, mRNA; synonyms: ACOX, PALMCOX, MGC1198; acyl-coenzyme A oxidase 1; Homo sapiens acyl-Coenzyme A oxidase 1, palmitoyl (ACOX1), transcript variant 2, mRNA.
202275_at	G6PD; G6PD; G6PD1	NM_000402	Xq28	Hs.802356	1.327344	Up	0.0089280358	1.1621786	Up	0.0823313	synonym: G6PD1; Homo sapiens glucose-6-phosphate dehydrogenase (G6PD), nuclear gene encoding mitochondrial protein, mRNA.
208369_s_at	GCDH	NM_013976	19p13.2	Hs.18414 1	1.178371	Up	0.0047789667	1.0740626	Up	0.0802165	Homo sapiens glutaryl-Coenzyme A dehydrogenase (GCDH), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.; Homo sapiens glutaryl-Coenzyme A dehydrogenase (GCDH), nuclear gene encoding mitochondrial protein, transcript variant 2, mRNA.

213818_x_at	COL6A1	AI862325	11	Hs.381134	1.562872	Up	3.03281E-05	1.1283788	Up	0.20423431	ESTe, Moderately similar to RIKEN cDNA 1810059G22 [Mus musculus] [M.musculus]
214892_x_at	NY-REN-24	BC004262	19p13.3	Hs.128425	1.290386	Up	3.8958E-05	1.0396883	Up	0.43972711	NY-REN-24 antigen
215588_x_at	HMGCL; HMGCL; HL	AL031295	1p36.1-p35	Hs.831	1.283746	Up	3.92631E-05	1.0334068	Up	0.5203439	synonym: HL; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria); Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria) (HMGCL), mRNA.
207606_at	TXNL2; TXNL2; PICOT	NM_006541	6p25.3	Hs.42844	1.375835	Up	0.005318749	1.0210081	Up	0.66528908	synonym: PICOT; PKC-interacting cousin of thioredoxin; Homo sapiens thioredoxin-like 2 (TXNL2), mRNA.
205236_x_at	SOD3	NM_003102	4p16.3-q21	Hs.2420	1.280517	Up	0.001685857	1.0086441	Up	0.88220476	Homo sapiens superoxide dismutase 3, extracellular (SOD3), mRNA.
203576_at	BCAT2; BCAT2; BCT2	NM_001190	19q13	Hs.101408	1.287101	Up	0.000421341	1.0767065	Up	0.19972362	synonym: BCT2; predicted mature protein begins at amino acid 28; Homo sapiens branched chain aminotransferase 2, mitochondrial (BCAT2), mRNA.
208581_x_at	MT1X	NM_005952	16q13	Hs.374950	1.547621	Up	0.010241902	1.3210147	Up	0.0043797	synonyms: MT1, MT-1I; Homo sapiens metallothionein 1X (MT1X), mRNA.

purine metabolism (matrix)

203722_at	ALDH4A1; ALDH4A1; P5CD; P5CDH; P5CDh; P5CDhL; P5CDhS	NM_003748	1P36	Hs.77448	1.432504	0.021808934	1.2840856	0.07248872 synonyms: P5CD, ALDH4, P5CDH, P5CDhL, P5CDhS; aldehyde dehydrogenase 4; mitochondrial delta-1-pyrroline 5-carboxylate dehydrogenase; P5C dehydrogenase; Homo sapiens aldehyde dehydrogenase 4 family, member A1 (ALDH4A1), nuclear gene encoding mitochondrial protein, transcript variant P5CDhL, mRNA.; synonyms: P5CD, ALDH4, P5CDH, P5CDhL, P5CDhS; aldehyde dehydrogenase 4; mitochondrial delta-1-pyrroline 5-carboxylate dehydrogenase; P5C dehydrogenase; Homo sapiens aldehyde dehydrogenase 4 family, member A1 (ALDH4A1), nuclear gene encoding mitochondrial protein, transcript variant P5CDhS, mRNA.

	202148_s_at	PYCR1; PYCR1; P5C; P5CR; PP222	NM_006907	17q25.3	Hs.79217	1.12087 Up	0.121662507	1.1226109 Up	0.08014123	synonyms: P5C, P5CR, PYCR, PP222; P5C reductase; Homo sapiens pyrroline-5-carboxylate reductase 1 (PYCR1), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.; synonyms: P5C, P5CR, PYCR, PP222; P5C reductase; Homo sapiens pyrroline-5-carboxylate reductase 1 (PYCR1), nuclear gene encoding mitochondrial protein, transcript variant 2, mRNA.
metallo proteins [illegible]	208581_x_at	MT1X	NM_005952	16q13	Hs.374950	1.347524 Up	0.010247903	1.321347 Up	0.0041797	synonyms: MT1, MT1; Homo sapiens metallothionein 1X (MT1X), mRNA.
	204326_x_at	MT1L	NM_002450	16q13	Hs.380776	1.623265 Up	0.017017251	1.232618 Up	0.0281237	synonyms: MT1, MT1R; metallothionein 1R; Homo sapiens metallothionein 1L (MT1L), mRNA.
	204745_x_at	MT1G; MT1G; MGC12386	NM_005950	16q13	Hs.433391	1.28968 Up	0.0322672	1.364678 Up	0.0358903	synonyms: MT1, MGC12386; Homo sapiens metallothionein 1G (MT1G), mRNA.
	206461_x_at	MT1H	NM_005951	16q13	Hs.2667	1.365586 Up	0.025668532	1.3155874 Up	0.0133935	synonym: MT1; Homo sapiens metallothionein 1H (MT1H), mRNA.
	211456_x_at		AF333388		Hs.367850	1.354488 Up	0.016339171	1.3367926 Up	0.0097776	MT-1H-like protein; mutant as compared to wild-type sequence MT-1H in GenBank Accession Number X64834; Homo sapiens metallothionein 1H-like protein mRNA, complete cds.

	212185_x_at	MT2A	NM_005953	16q13	Hs.118786	1.384172 Up	0.033675359	1.3559748 Up	*0.0171698*	synonym: MT2; This sequence comes from Fig. 2; Homo sapiens metallothionein 2A (MT2A), mRNA.
	212859_x_at	MT1E	BF217861	16q13	Hs.433205	1.34809 Up	0.012855859	1.2167657 Up	*0.023793*	metallothionein 1E (functional)
	217165_x_at	MT1F; MT1F; MGC32732	M10943	16q13		1.186389 Up	0.225324931	1.2547997 Up	*0.0079279*	synonyms: MT1, MGC32732; Homo sapiens metallothionein 1F (functional) (MT1F), mRNA.
	213629_x_at	MT1F	BF246115	16q13	Hs.381097	1.120311 Up	0.312657589	1.1835956 Up	*0.057089*	metallothionein 1F (functional)
Ornithine related	201599_at	OAT; OAT; HOGA	NM_000274	10q26	Hs.75485	1.210476 Down	0.003978229	0.8748833 Down	0.01912881	synonym: HOGA; Ornithine aminotransferase; Homo sapiens ornithine aminotransferase (gyrate atrophy) (OAT), nuclear gene encoding mitochondrial protein, mRNA.
	212461_at	OAZIN	BF793951	8q22.3	Hs.223014	1.239532 Down	*0.016483367*	1.1311716 Down	*0.0150402*	ornithine decarboxylase antizyme inhibitor
	201364_s_at	OAZ2	AF242521	15q22.1	Hs.74563	1.115702 Down	0.079801378	1.1385592 Down	*0.0359062*	protein translation dependent on +1 ribosomal frameshift; antizyme 2; Homo sapiens ornithine decarboxylase antizyme 2 (OAZ2), mRNA.
Arginine Related	203946_s_at	ARG2	U75667	14q24.1-q24.3	Hs.172851	1.241001 Down	0.00[illegible]	1.1794939 Down	*0.0080619*	kidney arginase; nonhepatic arginase; L-arginine amidinohydrolase; L-arginine ureahydrolase; AII; Homo sapiens arginase, type II (ARG2), nuclear gene encoding mitochondrial protein, mRNA.

	202262_x_at	DDAH2; DDAH2; G6a; NG30; DDAHII	NM_013974	6p21.3	Hs.24736 2	1.218874	Up	0.045169089	1.1140322	Up	0.06574631 synonyms: G6a, NG30, DDAHII; dimethylarginine dimethylaminohydrolase II; Homo sapiens dimethylarginine dimethylaminohydrolase 2 (DDAH2), mRNA.
ATP synthase (mitochondrial)	201089_at	ATP6V1B2; ATP6V1B2; HO57; VATB; VPP3; Vma2; ATP6B2; ATP6B1B2	NM_001693	8p22-p21	Hs.1697	1.203827	Down	0.008759781	0.8220404	Down	0.00155735 synonyms: HO57, VATB, VPP3, Vma2, ATP6B2, ATP6B1B2; vacuolar proton pump B isoform 2; endomembrane proton pump 58 kDa subunit; vacuolar ATP synthase subunit B, brain isoform; V-ATPase B2 subunit; H(+)-transporting two-sector ATPase, 56/58kD subunit, isoform 2; Homo sapiens ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B, isoform 2 (ATP6V1B2), mRNA.

201443_s_at	ATP6IP2; ATP6IP2; M8-9; APT6M8-9; ATP6M8-9	AF248955	Xq21	Hs.18343.4	1.138442	Down	0.01	9987098	0.8878037	Down	0.00772093	synonyms: M8-9, APT6M8-9, ATP6M8-9; ATPase, H+ transporting, lysosomal (vacuolar proton pump) membrane sector associated protein M8-9; vacuolar ATP synthase membrane sector associated protein M8-9; V-ATPase M8.9 subunit; ATPase membrane sector associated protein M8-9; renin receptor; Homo sapiens ATPase, H+ transporting, lysosomal interacting protein 2 (ATP6IP2), mRNA.
201444_s_at	ATP6IP2; ATP6IP2; M8-9; APT6M8-9; ATP6M8-9	NM_005765	Xq21	Hs.18343.4	1.302733	Down	0.0	12483331	0.7876111	Down	0.01120859	synonyms: M8-9, APT6M8-9, ATP6M8-9; ATPase, H+ transporting, lysosomal (vacuolar proton pump) membrane sector associated protein M8-9; vacuolar ATP synthase membrane sector associated protein M8-9; V-ATPase M8.9 subunit; ATPase membrane sector associated protein M8-9; renin receptor; Homo sapiens ATPase, H+ transporting, lysosomal interacting protein 2 (ATP6IP2), mRNA.

	202874_s_at	ATP6V1C1; ATP6V1C1; VATC; Vma5; ATP6C; ATP6D; FLJ20057	NM_001695	8q22.3	Hs.86905	1.244045 Down	0.012519633	0.8194812 Down	0.01590041	synonyms: VATC, Vma5, ATP6C, ATP6D, FLJ20057; vacuolar proton-ATPase, subunit C, V1 domain; H+-transporting ATPase chain C, vacuolar; vacuolar proton pump C subunit; H(+)-transporting two-sector ATPase, subunit C; vacuolar ATP synthase subunit C; V-ATPase C subunit; vacuolar proton pump, 42-kD subunit; vat c; H+ -ATPase C subunit; ATPase, H+ transporting, lysosomal, 42kD; ATPase, H+ transporting, lysosomal, subunit C; Homo sapiens ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C, isoform 1 (ATP6V1C1), mRNA.
ATP synthase (vacuolar)	202325_s_at	ATP5J; ATP5J; ATPM; ATP5A	NM_001685	21q21.1	Hs.73851	1.196518 Down	0.00068097	0.8946735 Down	0.00801154	synonyms: ATP5, ATPM, ATP5A; ATP synthase, H+ transporting (ATPase, mitochondrial); ATP synthase coupling factor 6; Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit F6 (ATP5J), nuclear gene encoding mitochondrial protein, mRNA.
	207607_s_at	ATP5G3	NM_001689	2q31.1	Hs.429	1.193118 Down	0.005733489	0.8544746 Down	0.00014404	ATP synthase, mitochondrial, C subunit-3; Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9) isoform 3 (ATP5G3), mRNA.

207509_at	ATP5G3	NM_001689	2q31.1	Hs.429	1.131785 Down	0.034321	0.8551774 Down	0.002336781	ATP synthase, mitochondrial, C subunit-3; Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9) isoform 3 (ATP5G3), mRNA.
208745_at	ATP5L	AA917572	11q23	Hs.10747 8	1.187675 Down	0.011545567	0.8447284 Down	0.00101299	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g
208670_x_at	ATP5C1; ATP5C1; ATP5CL1	BC000931	10q22-q23	Hs.15543 3	1.124441 Down	0.0193443046	0.8128323 Down	0.01392037	synonyms: ATP5C, ATP5CL1; H(heart)-type ATP synthase gamma-subunit; ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide-like 1; Homo sapiens ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1 (ATP5C1), mRNA.
211755_s_at	ATP5F1	BC005860	1p13.1	Hs.81534	1.162583 Down	0.003380778	0.8787933 Down	0.00153431	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit b, isoform 1
213738_s_at	ATP5A1	AI587923	18q12-q21	Hs.40598 5	1.144936 Down	0.009581883	0.8780464 Down	0.00365739	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit, isoform 1, cardiac muscle

complex I

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201304_at	NDUFA5; NDUFA5; B13; NUFM; UQOR13; FLJ12147; CI-13KD-B	NM_005000	7q32	Hs.83916	1.251252 Down	0.004318206	0.8638455 Down	0.01984249	synonyms: B13, NUFM, UQOR13, FLJ12147, CI-13KD-B; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5 (13kD, B13); Complex I-13KD-B; ubiquinone reductase; type I dehydrogenase; Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa (NDUFA5), nuclear gene encoding mitochondrial protein, mRNA.
202001_s_at	NDUFA6; NDUFA6; B14	NM_002490	22q13.2-q13.31	Hs.27441 6	1.190897 Down	0.002835277	0.8364085 Down	0.00056884	synonym: B14; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14kD, B14); Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa (NDUFA6), mRNA.
202077_at	NDUFAB1; NDUFAB1; SDAP	NM_005003		Hs.5556	1.178566 Down	0.001418435	0.8300824 Down	0.00023024	synonym: SDAP; NDUFAB1 subunit; NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1 (8kD, SDAP); Homo sapiens NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1, 8kDa (NDUFAB1), mRNA.

203371_s_at	NDUFB3; NDUFB3; B12	NM_002491	2q31.3	Hs.10978 0	1.193323 Down	0.007469942	0.83959 Down	0.00103955	synonym: B12; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3 (12kD, B12); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa (NDUFB3), mRNA.
203613_s_at	NDUFB6; NDUFB6; B17	NM_002493		Hs.10984 8	1.138507 Down	0.022368242	0.8259686 Down	0.00038684	synonym: B17; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6 (17kD, B17); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa (NDUFB6), mRNA.
203621_at	NDUFB5; NDUFB5; SGDH	NM_002492	3q27.1	Hs.19238	1.151694 Down	0.042430346	0.8951766 Down	0.01913904	synonym: SGDH; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5 (16kD, SGDH); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa (NDUFB5), mRNA.
208780_s_at	NDUFB1; NDUFB1; MNLL; CI-SGDH	NM_004545	14q32.12	Hs.18343 5	1.190237 Down	0.004989015	0.8718049 Down	0.00309562	synonyms: MNLL, CI-SGDH; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1 (7kD, MNLL); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa (NDUFB1), mRNA.

209303_at	NDUFS4; NDUFS4; AQDQ	BC005270	5q11.1	Hs.10758	1.15407 Down	0.02314134	0.833423 Down	0.00049245	synonym: AQDQ; NADH dehydrogenase (ubiquinone) Fe-S protein 4 (18kD) (NADH-coenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kD (NADH-coenzyme Q; mitochondrial respiratory chain complex I (18-KD subunit); Homo sapiens NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q reductase) (NDUFS4), mRNA.
217773_s_at	NDUFA4; NDUFA4; MLRQ	NM_002489		Hs.50098	1.185965 Down	0.005342988	0.869414 Down	0.00144106	synonym: MLRQ; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4 (9kD, MLRQ); Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa (NDUFA4), mRNA.
218101_s_at	NDUFC2; NDUFC2; B14.5b	NM_004549		Hs.183319	1.129474 Down	0.031751159	0.8888449 Down	0.00161606	synonym: B14.5b; NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2 (14.5kD, B14.5b); Homo sapiens NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa (NDUFC2), mRNA.
218226_s_at	NDUFB4; NDUFB4; B15	NM_004547	3q13.33	Hs.227750	1.118038 Down	0.018501169	0.9283017 Down	0.03138745	synonym: B15; NDUFB4 subunit; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4 (15kD, B15); Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa (NDUFB4), mRNA.

Complex 3

200883_at	UQCRC2	NM_003366	16p12	Hs.173554	1.213298 Down	0.00595247	0.8553081 Down	0.01997364	Homo sapiens ubiquinol-cytochrome c reductase core protein II (UQCRC2), mRNA. synonyms: QPC, QP-C, UQBC, UQBP, UQPC; Homo sapiens ubiquinol-cytochrome c reductase binding protein (UQCRB), mRNA.
205849_s_at	UQCRB; UQCRB; QPC; QP-C; UQBC; UQBP; UQPC	NM_006294	8q22	Hs.131256	1.185495 Down	0.012369038	0.8808683 Down	0.0017732	ubiquinol-cytochrome c reductase core protein II
212500_s_at	UQCRC2	AV727381	16p12	Hs.173554	1.116486 Down	0.039363536	0.8932686 Down	0.00788428	

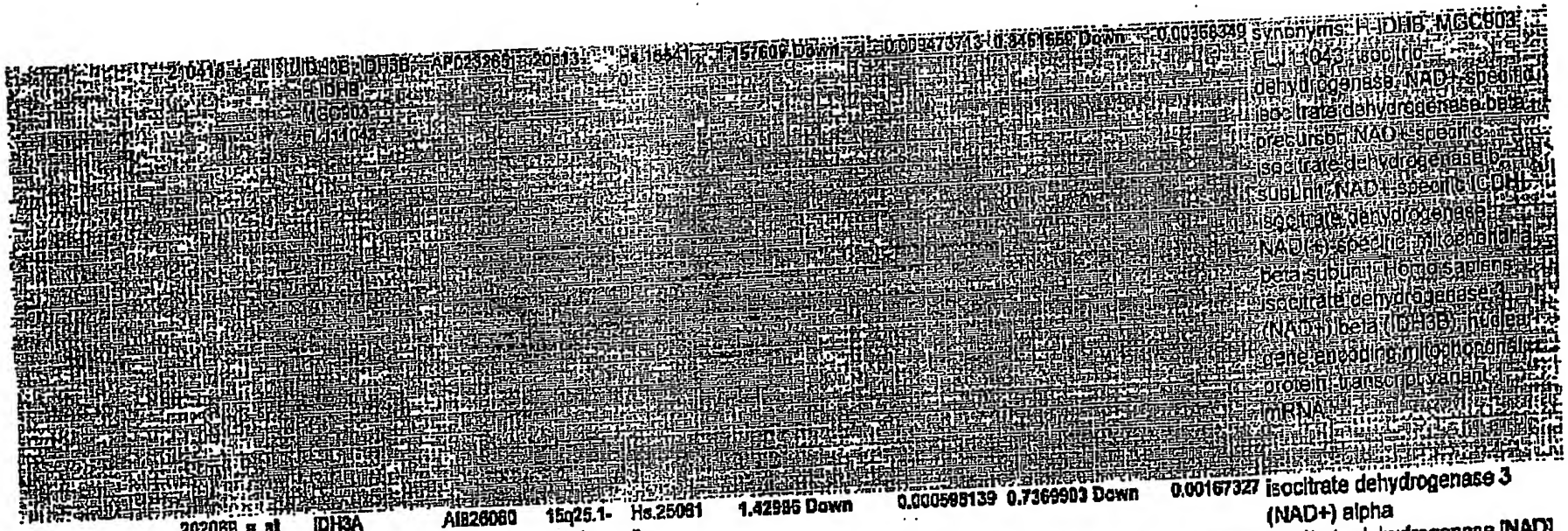
Complex 4

202110_at	COX7B	NM_001866	Xq13.2	Hs.432170	1.130844 Down	0.045735159	0.8629508 Down	0.00061257	synonyms: COX7A; COX7AL; COXVIIa-L; hepatic cytochrome c oxidase chain VIIa; Homo sapiens cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein, mRNA. cytochrome-c oxidase chain VIIb; Homo sapiens cytochrome c oxidase subunit VIIb (COX7B), nuclear gene encoding mitochondrial protein, mRNA.

	203663_s_at	COX5A; COX5A-VA; COX-VA	NM_004255	15q25	Hs.[illegible]	1.197[illegible] Down	0.00437[illegible]	0.8[illegible] Down	[illegible]E-05	synonyms: VA, COX, COX-VA; cytochrome c oxidase polypeptide, mitochondrial precursor; Homo sapiens cytochrome c oxidase subunit Va (COX5A), nuclear gene encoding mitochondrial protein, mRNA.
	203880_at	COX17	NM_005694		Hs.16297	1.198099 Down	0.014912612	0.8134966 Down	0.00016529	human homolog of yeast mitochondrial copper recruitment gene; COX17 (yeast) homolog, cytochrome c oxidase assembly protein; Homo sapiens COX17 homolog, cytochrome c oxidase assembly protein (yeast) (COX17), nuclear gene encoding mitochondrial protein, mRNA.
	214277_at	COX11	AI376724	17q22	Hs.241515	1.287588 Down	0.009150853	0.8605178 Down	0.02984133	COX11 homolog, cytochrome c oxidase assembly protein (yeast)
	217491_x_at	COX7CP1	AF042165	13q14-q21		1.148912 Down	0.031232884	0.8439594 Down	0.04448098	cytochrome c oxidase subunit VIIc; E.C. number =1.9.3.1; Homo sapiens cytochrome c oxidase subunit VIIc (COX7CP1) pseudogene, complete sequence.
	217329_x_at	COX7BP1; bK714B7.1	AF042164	22q13		1.228784 Down	0.002837439	1.1261074 Down	0.08248036	cytochrome c oxidase subunit VIIb; E.C. number =1.9.3.1; Homo sapiens cytochrome c oxidase subunit VIIb (COX7BP1) pseudogene, complete sequence.
Holocytochrome c Synthetase	203745_at	HCCS	AI801013	Xp22.3	Hs.211571	1.168718 Down	0.002771728	0.8395424 Down	0.00836825	holocytochrome c synthase (cytochrome c heme-lyase)

	203746_s_at	HCCS; HCCS; CCHL	NM_005333	Xp22.3	Hs.21167 1	1.192373 Down	0.005742037	0.8000534 Down	0.01929721	synonym: CCHL; putative; Homo sapiens holocytochrome c synthase (cytochrome c heme-lyase) (HCCS), mRNA.
Adenine translocators [redacted]										
33 Glycine/Serine metabolism	204294_at	AMT; AMT; GCE; NKH; GCST	NM_000481	3p21.2-p21.1	Hs.102	1.20989 Up	0.003991538	1.0981119 Up	0.01028424	synonyms: GCE, NKH, GCST; Homo sapiens aminomethyltransferase (glycine cleavage system protein T) (AMT), mRNA.
Voltage dependant anion channels [redacted]										
	217140_s_at	VDAC1P	AJ002428	Xq21-q22		1.215466 Down	0.018102094	0.7707105 Down	0.0008454	Homo sapiens VDAC1 pseudogene.
	208846_s_at	VDAC3; VDAC3; HD-VDAC3	U90943	8p11.2	Hs.7381	1.150067 Down	0.080742368	1.1200838 Down	0.0287343	synonym: HD-VDAC3; similar to mouse VDAC 3; Homo sapiens voltage-dependent anion channel 3 (VDAC3), mRNA.

Lactate metabolism	213564_x_at	LDHB	BE042354	12p12.2-p12.1	Hs.23448 9	1.104588 Down	0.030076871	0.9133205 Down	0.00138514	lactate dehydrogenase B
	200650_s_at	LDHA; LDHA; LDH1	NM_005566	11p15.4	Hs.2795	1.134901 Down	0.03774399	1.1884696 Down	0.000774	synonym: LDH1; Homo sapiens lactate dehydrogenase A (LDHA), mRNA.
	201030_x_at	LDHB	NM_002300	12p12.2-p12.1	Hs.23448 9	1.08367 Down	0.03827143	1.1007107 Down	0.0010265	Homo sapiens lactate dehydrogenase B (LDHB), mRNA.
Isocitrate dehydrogenase	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]



202068_s_at	IDH3A	AI826060	15q25.1-q25.2	Hs.25091 6	1.42986 Down	0.000598139	0.7369903 Down	0.00167327	isocitrate dehydrogenase 3 (NAD+) alpha
202070_s_at	IDH3A	NM_005530	15q25.1-q25.2	Hs.25091 6	1.107756 Down	0.098643023	1.1153047 Down	0.0234165	isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial; NAD+-specific ICDH; NAD(H)-specific isocitrate dehydrogenase alpha subunit precursor; isocitrate dehydrogenase (NAD+) alpha chain precursor; H-IDH alpha; isocitric dehydrogenase; Homo saplens isocitrate dehydrogenase 3 (NAD+) alpha (IDH3A), nuclear gene encoding mitochondrial protein, mRNA.

35

HMG related

	216588_x_at [illegible]	HMGCL; HL; HMGCL; HL	AL031295	1p36 [illegible]	Hs.[illegible]	1.283743 Up	[illegible]	[illegible]	synonym: HL; 3-hydroxy-3-methylglutaryl-Coenzyme A lyase; 3-hydroxy-3-methylglutaryl-coenzyme A lyase (hydroxymethylglutaricaciduria); Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria) (HMGCL), mRNA.
	202540_s_at	HMGCR	NM_000859 5q13.3-q14	Hs.11899	1.237843 Down	0.004508094	0.8558926 Down	0.02049312	Homo sapiens 3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMGCR), mRNA.
Glutamate metabolism	219933_at	GLRX2; GLRX2; GRX2	NM_016066 1q31.2-q31.3	Hs.[illegible]	1.21[illegible] Down	0.00[illegible]	0.8[illegible] Down	0.000[illegible]	synonym: GRX2; thioltransferase; contains nuclear membrane localization; CGI-133 protein; Homo sapiens glutaredoxin 2 (GLRX2), mRNA.
Oxidorelated	202017_at	EPHX1; EPHX1; MEH; EPOX	NM_000120 1q42.1	Hs.89649	1.406022 Up	0.065587794	1.4165663 Up	0.0222559	synonyms: MEH, EPHX, EPOX; Epoxide hydroxylase 1, microsomal (xenobiotic); Homo sapiens epoxide hydrolase 1, microsomal (xenobiotic) (EPHX1), mRNA.

Claims

1. A method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the expression level of the majority of the following genes, or the levels of the majority of the proteins encoded by the following genes in a biological sample obtained from the subject, or in a sample derived from a biological sample obtained from the subject: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

2. A method according to claim 1, wherein the biological sample comprises a peripheral tissue or cell type in which the level of the protein, or the expression level of the gene, correlates with the level of the corresponding protein, or the expression level of the corresponding protein, in the prefrontal cortex.

3. A method according to claim 2, wherein the peripheral tissue or cell type comprises a blood cell.

4. A method according to claim 4, wherein the blood cell is a macrophage, a monocyte, a lymphocyte, an erythrocyte, a platelet, a leukocyte (either a neutrophil, an eosinophil, or a basophil; a lymphocyte, or a monocyte).

5. A method of prevention, treatment, or amelioration of schizophrenia which comprises increasing the level or activity of the majority of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2;

MPPE1; and reducing the level or activity of the majority of the following proteins in the brain (in particular the prefrontal cortex) of the subject: FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

6. A gene chip for use in a method of diagnosis according to any of claims 1 to 4, the gene chip comprising a plurality of different probes capable of hybridising to nucleic acid expression products of the majority of the following genes: PARG; VDAC2; OLR1; ARPC3; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; FBS1; WFS1; PRODH; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

7. Use of a gene chip according to claim 6 in a method of diagnosis of schizophrenia.

Mitochondrial Changes

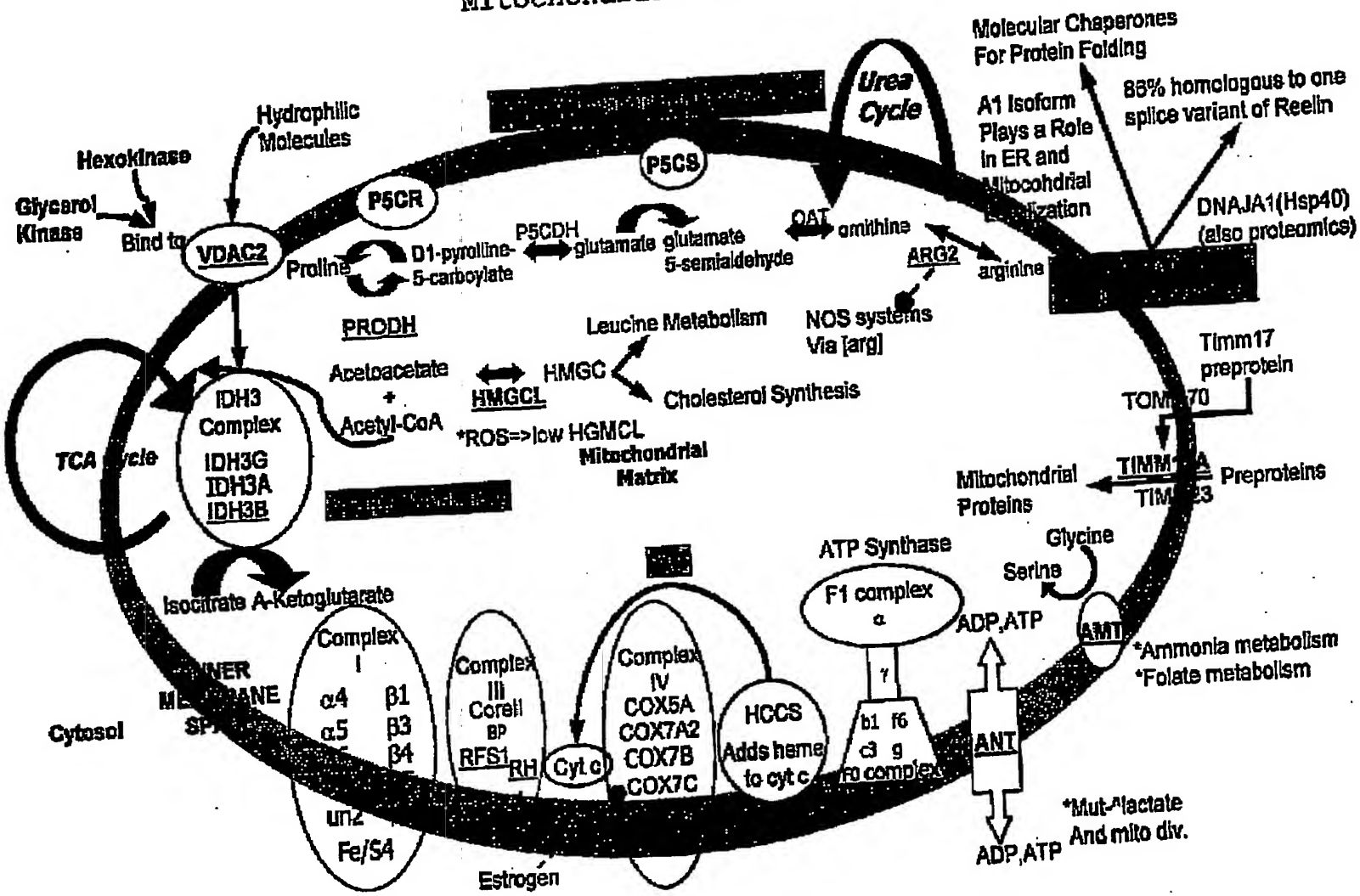


Figure 1

Figure 2

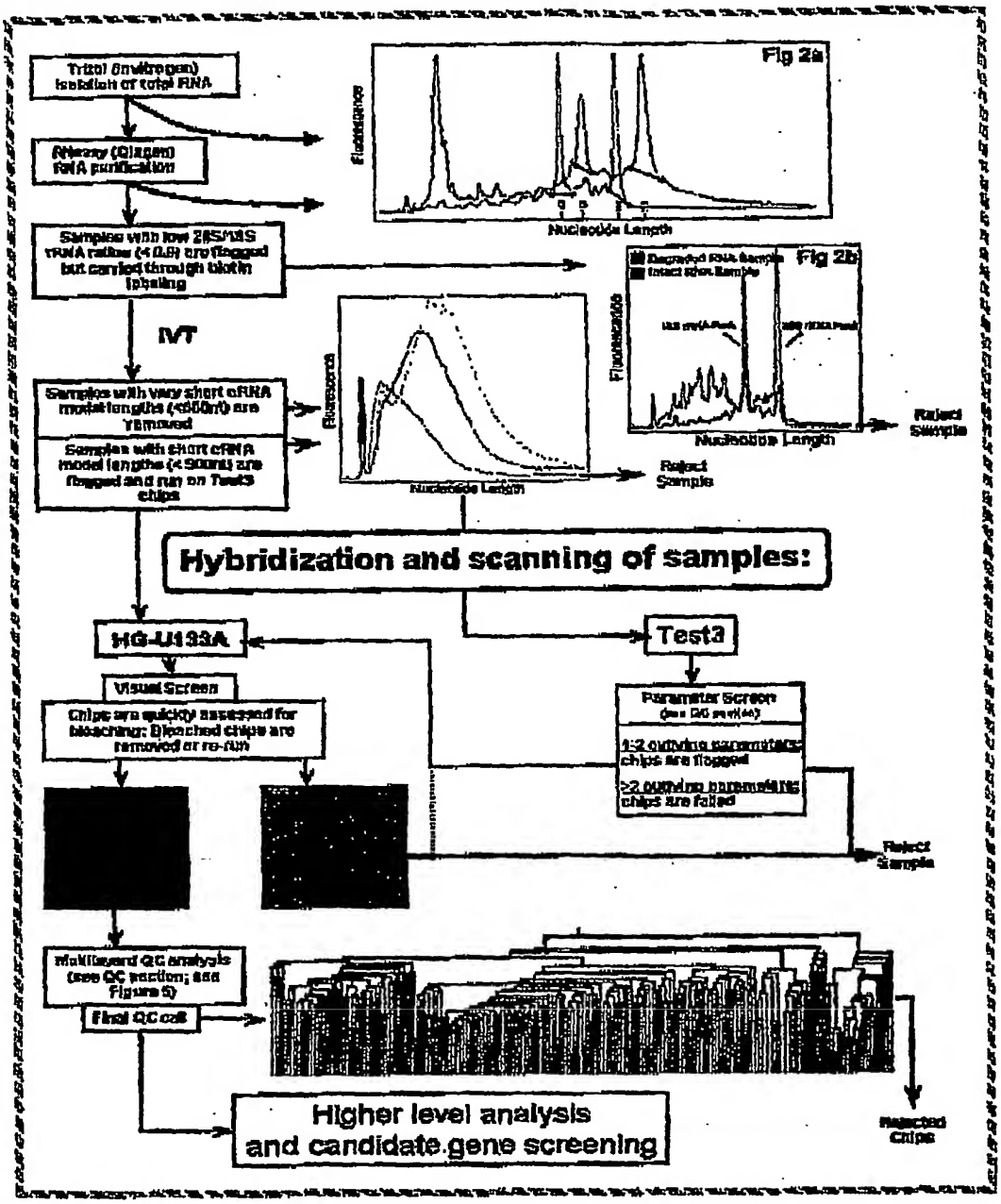

Trizol (Invitrogen) isolation of total RNA
RNeasy (Qiagen) RNA purification
Samples with low 28S/18S rRNA ratios (<1.0) are flagged but carried through biotin labeling
IVT
Samples with very short cRNA modal lengths (<600nt) are removed
Samples with short cRNA modal lengths (< 900nt) are flagged and run on Test3 chips
Fig 2a
Fluorescence
Nucleotide Length
Fig 2b
Degraded RNA Sample
Intact RNA Sample
Reject Sample
Hybridization and scanning of samples:
HG-U133A
Test3
Visual Screen
Chips are quickly assessed for bleaching; Bleached chips are removed or re-run
Parameter Screen
1-2 outlying parameters: chips are flagged
>2 outlying parameters: chips are failed
Reject Sample
Multilayered QC analysis (see QC section; see Figure 5)
Final QC call
Higher level analysis and candidate gene screening
Rejected Chips

Figure 3

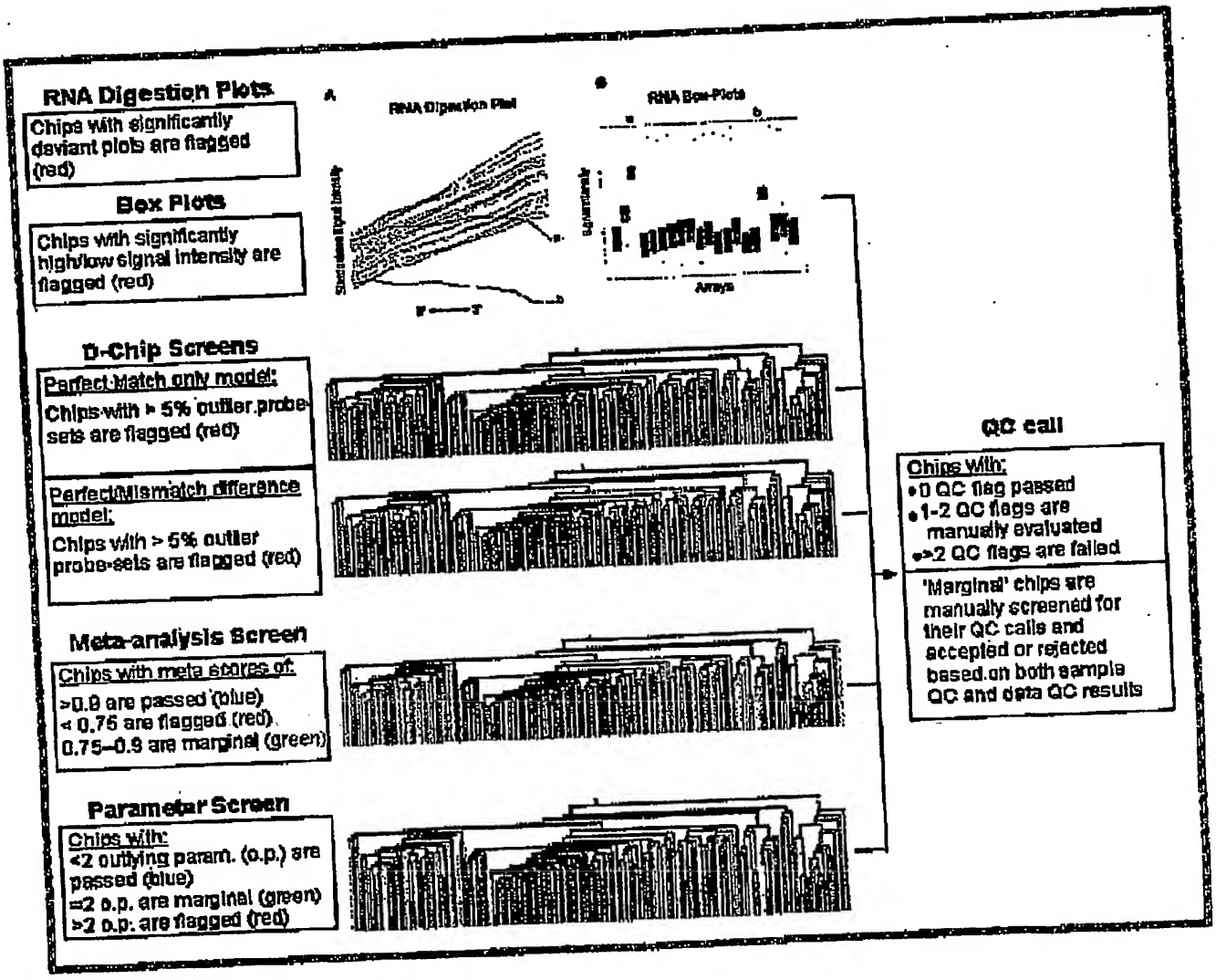

RNA Digestion Plots
Chips with significantly deviant plots are flagged (red)
Box Plots
Chips with significantly high/low signal intensity are flagged (red)
D-Chip Screens
Perfect Match only model:
Chips with > 5% outlier probe-sets are flagged (red)
Perfect/Mismatch difference model:
Chips with > 5% outlier probe-sets are flagged (red)
Meta-analysis Screen
Chips with meta scores of:
>0.9 are passed (blue)
< 0.75 are flagged (red)
0.75–0.9 are marginal (green)
Parameter Screen
Chips with:
<2 outlying param. (o.p.) are passed (blue)
=2 o.p. are marginal (green)
>2 o.p. are flagged (red)
QC call
Chips with:
• 0 QC flag passed
• 1-2 QC flags are manually evaluated
• >2 QC flags are failed
'Marginal' chips are manually screened for their QC calls and accepted or rejected based on both sample QC and data QC results

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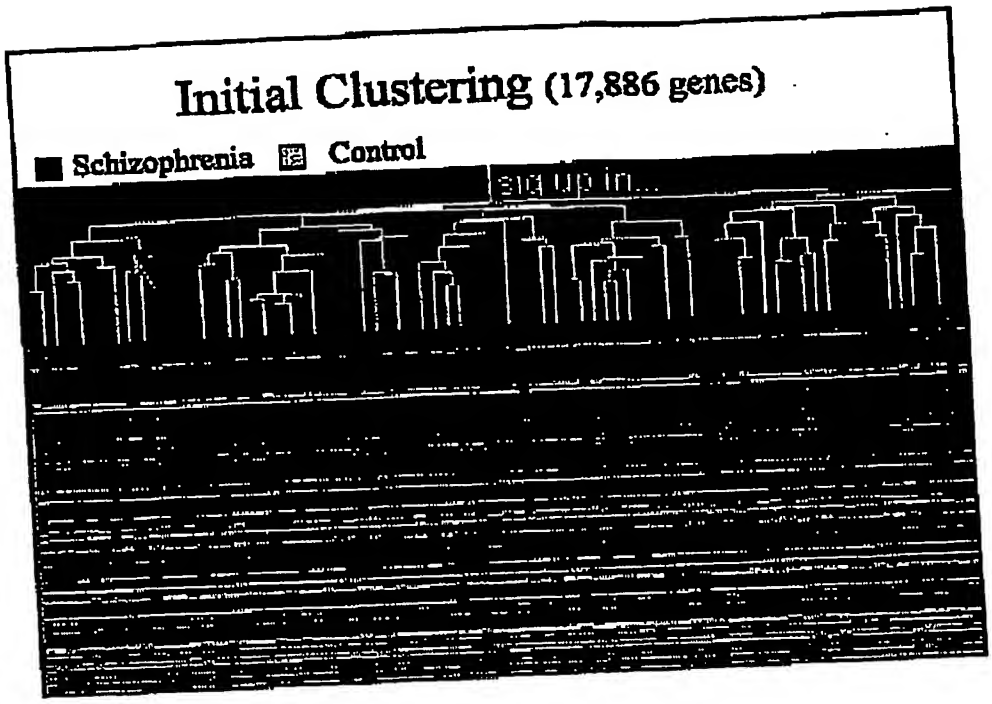
Figure 4


Initial Clustering (17,886 genes)
Schizophrenia
Control
sig up in...

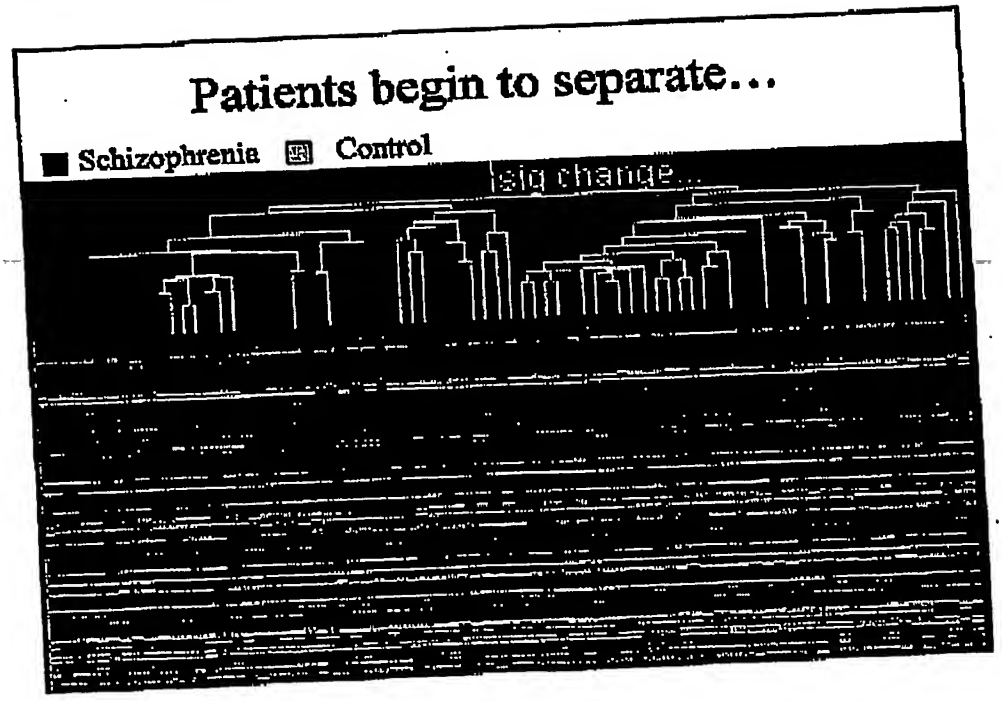

Patients begin to separate...
Schizophrenia
Control
sig change...

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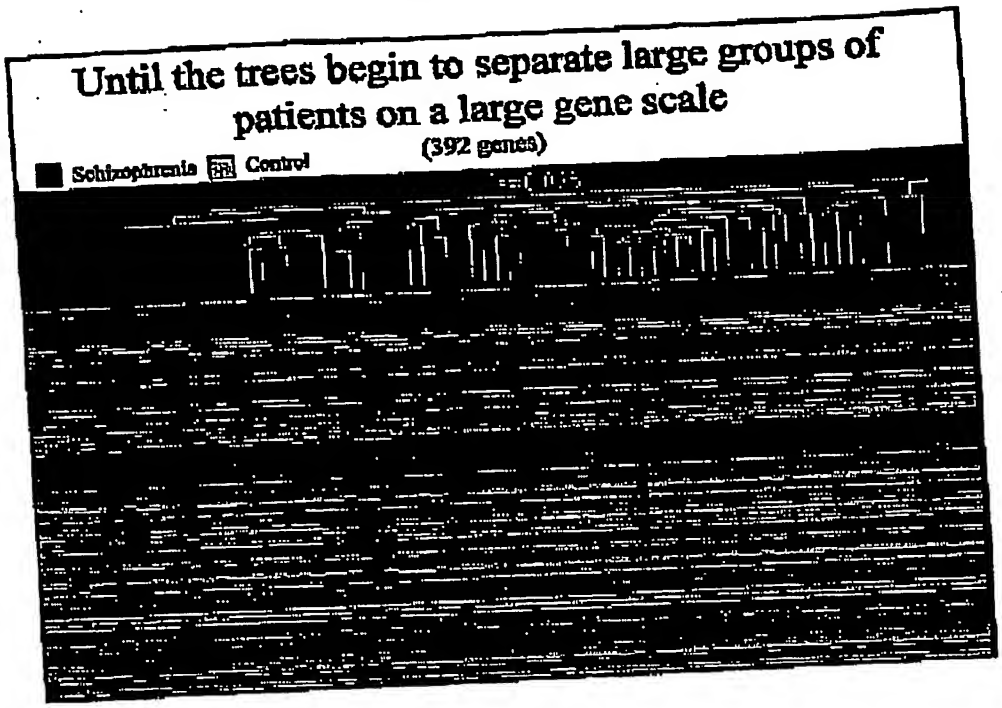
Figure 5


Until the trees begin to separate large groups of patients on a large gene scale
(392 genes)
Schizophrenia
Control

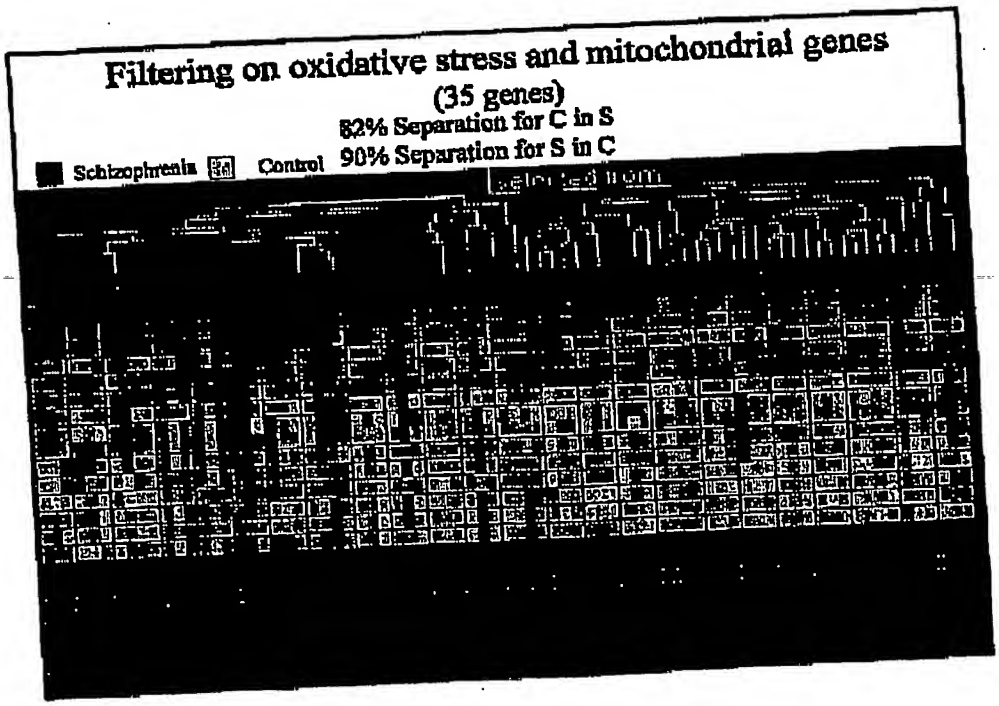

Filtering on oxidative stress and mitochondrial genes
(35 genes)
82% Separation for C in S
90% Separation for S in C
Schizophrenia
Control

Figure 6

Oxidative Buffering